THE ESSENTIAL STRUCTURAL FEATURES OF DDT (1-trichloro-2,2-bis-(p-chlorophenyl)-ethane) DETERMINED BY A STUDY OF THE INSECTICIDAL ACTIVITY OF CLOSELY RELATED COMPOUNDS

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JEAN PAUL PICARD

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Introduction

In attempts to explain the essential structural features of DDT (1-trichloro-2,2-bis-(p-chlorophenyl)trichloroethane several theories have been proposed.

Lauger *et al.* (1944) postulated the necessity of $=CHCCl_3$ group, as a lipophylic agent, in the DDT molecule in order for this type of compound to be effective as insecticide. They claimed that this group causes the molecule to have an affinity for nerve lipoids. The extreme toxicity is governed by the p-bridged 4,4′-disubstituted rings, which act as an enzyme-blocking mechanism.

On the basis of the inactivity of 4,4′-dichlorobenzophenone and 4,4′-dichlorodiphenylacetic acid, Martin and Wain (1944) have associated the toxicity of the DDT-type compound with the ease with which the $=CHCCl_3$ dehydrohalogenates at the site of action, assuming that the molecule is stable enough to survive translocation. The same authors have also pointed out that there was no apparent relationship existing between the effectiveness of the compounds and the electronic effects (electromeric and inductive) of the substituents in the 4,4′ positions. Along the same line, Fleck and Haller (1944) have reported that DDT readily loses hydrogen chloride in the presence of a naturally occurring catalyst.

A more recent concept, but still ill-defined, is the spatial relationship of the different parts of the molecule to one another. This has been considered as the most important factor by Gunther and Metcalf (1946).

In view of these facts eight analogs of DDT molecule were synthesized and compared to closely related compounds in which the $=CHCCl_3$ of the former was replaced by $=C=O$ and successively by $=CHOH$.

Methods

A quantitative measurement of the relative potency of

each compound prepared, was accomplished by determining the amount of the compound, in milligrams per 929 cm^2, required to kill 50% male german roaches continuously exposed for 96 hours to surfaces coated with the compound. This amount was called the L.D. 50 (lethal dose to kill 50%) for 96 hours exposure.

The actual testing of the material was carried out by coating half-pint jars with acetone solutions containing various concentrations of the compound to be tested. The total surface area of a jar was found to be 336 cm^2. Knowing the surface area to be coated, the concentration of the solution to be used, and the number of mgs/929 cm^2 desired, the proper volume of the acetone solution was added to the jars by means of a .05-cc. graduated burette. The jars were uniformly coated by rotating them by hand until complete evaporation of the acetone solution. Ten male german roaches after anesthesia with carbon dioxide were confined in each jar and a minimum of ten jars was prepared for each concentration to be tested.

The insect used in this experiment was the adult male of german roach *Blatella germanica* (L.). This insect was selected on the basis of its readily availability and the ease with which it could be reared. As many as 14,000 male adult roaches were used in the present study.

The same compounds have also been evaluated as contact insecticidal sprays, by using a rather recent apparatus for testing such material which is called the "Wind Tunnel Method."

The material to be tested is dissolved to the proper concentration in a highly refined kerosene ("Deo-base"). The volume of the spray solution is 0.5 cc. Checks run with 0.7 cc. of "Deo-base" alone gave less than 5% mortality.

The insects used for these evaluations were 4-days old house flies *Musca domestica* (L.). They were reared according to the specifications given in the Soap Blue Book, 1946.

Results

The replacement of $=CHCCl_3$ by $=CHOH$ in the 4,4′-disubstituted analogs of DDT in which both substituents were fluorine chlorine, bromine, methyl and methoxy appear to be as toxic to male german roaches as the parent compound.

The same is true of the analog without substituent in either rings although a considerable decrease in activity is apparent.

On the basis of the tests performed it is possible to establish the relative order of potency of these most active analogs of DDT and related compounds, by comparing their L.D. 50's. These comparisons were made by plotting on logarithmic-probability paper the per cent mortality of male roaches exposed to various concentrations of these compounds for 96 hours. The amount required by each compound to kill 50% roaches or the L.D. 50, can be directly obtained from the Dosage-Mortality Curves.

The 4,4′-diethoxy and the 4,4′-diethyl analogs of DDT have also been tested, but their L.D. 50 was 35 mgs/929 cm^2 and 29 mgs/929 cm^2 respectively. Due to their low activity the hydrol derivatives of these two compounds were not prepared.

The benzophenone derivatives have been tested at ten times the concentration required by their parent compound to kill 50% roaches, but even at that high concentration none of them show any signs of activity.

Conclusion

The high activity of the hydrol corresponding to the DDT analogs, leads one to believe that the lipoid soluble group ($CHCCl_3$) is not necessarily required in order for the DDT-type compound to be active and that a molecule of this type, deprived of its ability of losing hydrogen chloride, could still act as an insecticide.

In regard to insecticidal activities, the compound must be substituted in the 4,4′-postions, as demonstrated by the low activity of the unsubstituted analogs, and the substituents must be of a limited size. This point is well elucidated by the low L.D. 50's found for the 4,4′-dimethoxyl and 4,4′-dimethyl compounds as compared with their next higher homologs. The difference is about ten fold.

The fact that toxicity in the DDT analogs vanished with the increase in the p-alkyl or p-alkoxyl substituents, indicates that enhanced paraffinic character is not beneficial even if it favors oil-solubility of the products.

The variation in toxicity within the 2,2-disubstituted ethanes, the difference in activity between the benzohydrol derivatives, and the inactivity of the benzophenones, when tested on two different groups of insects, suggest that the electronegative character of the substituents and the lipophylic action of the $=CHCCl_3$ group can not alone account for the significant action of this general type of structure, but rather the whole shape of the molecule must be considered. A mere mechanical view of tissue penetration by any contact poison leads to this consideration. This is also supported by the fact that molecules other than a certain size, were found to possess low activity. The non-requirement for the molecule to bear a $=CHCCl_3$ group supports also this view.

These findings tend to demonstrate the importance of exploring the potency of related compounds on more than one species of insects, before postulating the relationship between the chemical structure and toxicity. This point is strikingly illustrated by the high activity of the hydrols on the german roach and their relative inactivity when applied to the house fly.

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VITA

Jean P. Picard was born August 25, 1920 in Quebec, Canada. He received his grammar school and secondary school at the Commercial Academy of Lorette-ville, Quebec. In 1938 he enrolled at the Duchesnay School of Forestry where he graduated in 1940. In June 1940 he was employed as an entomological assistant by the Department of Lands and Forests, Quebec, with the understanding to be sent to the University of Illinois for Specialization in Entomology. During the winter 1940 and 1941 he attended courses of the Biological Division of Laval University, Quebec, in view of his further studies. He entered the University of Illinois in September 1942. He received his B. S. degree with a major in Entomology in June 1944. In September 1944 he continued his education at the University of Illinois on a first year graduate scholarship in the Department of Entomology. He received a M. S. degree in Entomology in June 1945. He continued his entomological training in October 1946 on a first year graduate fellowship in Entomology at the same institution. He attended school on a second year graduate fellowship in Entomology from September 1946 until October 1947.

He is a member of Phi Beta Kappa, Pi Mu Epsilon, Phi Sigma, the American Chemical Society and an associate member of Sigma Xi. He also belongs to the American Association of Economic Entomologists.